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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/042,460	03/16/1998	GREGG B. MORIN	015389003110	5004

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/26/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/042,460	MORIN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9,20-28 and 31-34* is/are pending in the application.

4a) Of the above claim(s) *5 and 9* is/are withdrawn from consideration.

5)☒ Claim(s) *21,22,24,25 and 27* is/are allowed.

6)☒ Claim(s) *20,23,26,28 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *42,46* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response and Dr. Morin's declaration filed on 06/12/03 has been acknowledged.

Claims 5, 32-34 are amended.

Claims 5, 9, 20-28 and 31-34 are pending.

This application contains claims 5 and 9 are drawn to an invention nonelected with traverse in Paper No. 15. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 20-28 and 31-34 are examined in this office action

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

►*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm).*

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by an application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: After applicant's amendment on 02/14/00 the instant application claims priority only to US App. No. 08/979,742 filed 11/26/97, and not to the other US or PCT applications as stated in the declaration. Appropriate correction is required.

The applicant fails to correct this defect in the response filed on 0612/03

Claim Objections

Claims 32-34 stand objected to because of the following informalities: The instant claims recites limitation "shown in figure 5" and fails to recite the required SEQ ID NO.

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application (see MPEP 2422.03).

The applicant fails to correct this defect in the response filed on 06/12/03. The applicant fails to provide an individual SEQ ID NO for each Motif (as claimed) in the context. The recent amendment designated a single SEQ ID NO for each motif (Motif-T, Motif-1, Motif-2, Motif-A, Motif-b, Motif-C and Motif-D). Identification of each motif by an individual SEQ ID NO has been suggested. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 20, 23, 26 and 31-34 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide encoding mouse mTERT protein wherein the protein has at least 90% sequence identity to SEQ ID NO:2, and the protein contains mouse Motif- T, Motif-1, Motiff-2, Motiff-A, Motiff-B, Motiff-C and Motiff-D and has telomerase catalytic activity when associated with telomerase RNA component, does not reasonably provide enablement for any natural and/or non-natural TERT proteins that have at least 90% sequence identity to SEQ ID NO:2 and has telomerase catalytic activity when associated with a telomerase RNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims, for the same reasons of record as set forth in the official action mailed on 02/10/03.

Response to arguments

The applicant argues that the instant application provides mouse TERT (SEQ ID NO:2) and based upon this prototype sequence it is routine matter for the skilled reader to make functional variants that are at least 90% identical. The applicant argues that specification

discloses family of sequence that are at least 60% identical to mTERT of which SEQ ID NO:2 is exemplary (response, page 6). The applicant argues that for the claims under examination in this application, the proper inquiry is not how many possible variants are there that have the specified structure but whether there are screening methods available at the time of filing that would allow the skill artisan to obtain variants without undue experimentation. Citing various published articles the applicant argues that a change to particular residues appears to affect telomerase activity don't establish that motifs shows in fig-5 are intolerant to mutations of any kind (response, page 8, para.1-2). The applicant argues that Dr. Morin's declaration states considerable variation in sequence can be accommodated without losing the TERT function. The applicant argues that since 42 of the 63 residues in the motif sequences has been changed during the course of evolution, experimental mutation studies are expected to show even more plasticity (response, page 8 para.3). The applicant argues that the declaration provides a straightforward protocol by which someone skilled in the art could obtain any number of functional TRT variants. The applicant concluded that Dr. Morin's declaration reinforces applicant's position that the variation claimed herein comes within the disclosure as filed based upon wands standard for routine experimentation (response, page 9).

However, this is found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). In instant case screening of any and all natural and non-natural telomerasere reverse transcriptase variants, wherein at least 10% amino acid are added substituted and/or deleted in the disclosed SEQ ID NO:2 is not considered routine n the art. The applicant fails to point out where in the specification there is support for extensive making and testing of any and all natural and non-natural variants of telomerase as claimed. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein at least 10% amino acids are added, deleted and/or substituted. The number of possible scenarios increase geometrically with increase in percent non-identity. For example 10% variation in SEQ ID N:2 (1122 amino acids) would lead to making and testing at least $2.8X10^9$ combinations which encompasses a change in single amino acid sequences (point mutation) to multiple amino acid sequences (112 amino acids) in any and all combinations. These variations encompass changes in conserved motifs that would render the screening of mutants highly unpredictable since the telomerase

activity is elicited by the telomerease-complex and not by mTERT alone (see Lundblad et al). Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to teach how to make the variants as claimed. Thus one has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed telomerase activity.

Furthermore, the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The scope of instant claims encompass an isolated nucleic acid molecule encoding a telomerase reverse transcriptase protein and its natural or non-natural variants, wherein 10% of amino acid sequences are added, deleted or substituted over the entire length. The variation as claimed also encompasses the conserved motifs that are germane to the telomerase reverse transcriptase activity. The state of the art clearly teaches that the functional activity telomerase-complex is complex, which involves interaction among TERT protein, RNA component and other TRT associated proteins. Furthermore TERT protein consists of several conserved motifs that are required for the telomerase activity (Lundblad, PNAS 95:8415-8416, 1998, *ref of record*). Besides the amino acids sequences of SEQ ID NO:2, the instant specification fails to disclose a single variant of SEQ ID NO:2, wherein addition, substitution or deletion of 10% of amino acid sequences in any of the disclosed TERT motifs or non-motif sequences did not altered the mTERT activity explicitly or implicitly as putatively considered by the applicant. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The variants as claimed are simply hypothetical proteins because no biological function has been established. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994. Rudinger in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976).

The courts have clearly stated that: "A specification did not disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). The general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997). Furthermore, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In instant case the extensive making and testing is nothing more than an invitation to further experimentation, since the specification can't be relied on to teach how to make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed telomerase activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed, since the applicant has not presented enablement commensurate in scope with the claims.

Claim 28 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use** the invention, for the same reasons of record as set forth in the official action mailed on 02/10/03.

Response to arguments

The applicant argues that making a knock out animals is routine in the art (response, page 9 para.3). The applicant further argues that specification provides illustration of how an exemplary targeting vector could be made that can be further used to make a mouse cell having inactivated endogenous TERT gene. The applicant argues that Dr. Choy Pik Chiu's declaration confirms that there are not unexpected difficulties in the making go TERT knockout mice. The applicant argues that instant invention relates to a product claim and the instant specification clearly teaches how to make a mouse cell with an altered endogenous TERT gene either by directly targeting cells in vitro or by harvesting altered cells from genetically altered mice (response, page 10).

However, this is found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record. The scope of instant claim encompasses a cell that has been transformed in vivo, therefore the invention as claimed not only falls in the realm of transgenic art but also relates to gene therapy (See MPEP § 2111 - § 2111.01). The state of art clearly teaches that the i) delivery of a gene of interest to any cell in vivo using any and all viral and or non-viral vectors and ii) making a transgenic animal has been considered highly unpredictable. The specification fails to disclose the delivery of polynucleotides as claimed in-vivo using viral or non-viral vectors via any and all routes of administration. In addition the scope of invention as claimed not only encompass an isolated mouse cell but also include a mouse cell derived from a transgenic mouse (*which is non-elected subject matter, see office action 07/05/00, page 2*) wherein the endogenous mTERT gene has been mutated. The applicant even fails to disclose a single transfected cell **(in-vitro)** wherein the endogenous mTERT gene in a cell has been mutated by recombinant mean. **At best example-4 teaches the electroporation of pmTERTKO vector in to WW6 ES cells but falls short of disclosing a single cell clone**

wherein the mTERT gene has been mutated (see example-4, page 114, line 27-31). Similarly, the specification proposes the injection of WW6 ES clones into C57BL/6 blastocytes, wherein the mTERT gene has been knocked out but fails to disclose a single founder animal exhibiting the required phenotype. In addition, Dr. Choy-Pik Chiu's declaration relies on publications that were published after the filing date of instant application, which does not enable instant specification for full scope of invention as claimed. A genetically engineered cell (in-vivo) wherein an endogenous mTERT gene has been muted by any recombinant means (by method of gene therapy or by any transgenic knock-out technique) has been not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

Claims 20, 23, 26, 28 and 31-34 are rejected.

Claims 21-22, 24-25 and 27 are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

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